AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,235	08/27/2001	Girish Sahni	Q89732	5356

23373 7590 02/10/2006

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,235	SAHNI ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Applicant's response of November 23, 2005 is acknowledged. It is acknowledged that Applicants have cancelled all pending claims and added Claims 34-54. Claims 34-54 are hereby examined.

Specification-Objections

Amendment of the specification on page 8, paragraph 2, to include the references Young et al, 1995 and Jackson et al, 1986, is acknowledged. However, said amendment is improper, as it introduces New Matter. Neither the specification nor an original Information Disclosure Statement discloses said references.

The specification is objected because the table on page 57 should be amended to provide a table number and correct the formatting of the data.

The specification is objected to for failing to identify the sequences disclosed in the specification by sequence identifier numbers (SEQ ID NO:). 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. The sequence listing discloses 24 sequences. The specification fails to identify any of the sequence disclosed therein by any of said sequence identifier numbers (SEQ ID NO:). Correction is required.

The specification is objected to for referring to a figure, without indicating which figure. Page 55, lines 15 and 17, comprise the term "Fig. ", without a number. Correction is required.

Abstract

The abstract of the disclosure is objected to because the first phrase is not a complete sentence.

Drawings

Figures 3, 6, 11, 14, 17, 19, 21, and 22 are objected to for not providing sequence identifier numbers (SEQ ID NO:) for the sequences disclosed in said figures. Correction of said drawings, or the legends thereto, is required.

Figure 3 is objected to for improper labeling. The two panels of Figure 3 are labeled "FIG. 3-1" and "FIG. 3-2". Said labeling is inconsistent with standard formatting; wherein said panels should be labeled "FIG. 3A" and "FIG. 3B". Correction is requested.

Figure 6 and its legend are objected to for the following reasons. The legend to Figure 6 asserts that the figure discloses the polynucleotides encoding each of five fibrin binding domains, FBD(1-5)-encoding DNAs, "obtained from EMBL; the file and accession no.'s are ID-HSFIBI and X02761, K00799, K02273, X00307, X00739". However, Figure 6 discloses only a single sequence. Furthermore, the polynucleotide disclosed by EMBL accession number ID-HSFIBI is annotated as a DNA sequence surrounding human nuclear factor I binding site, not a fibrin binding domain (see enclosure). Clarification is required.

Figure Legends

The figure legends are objected to for the following reasons.

Fig 4: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 4 is derived, should be stated.

Fig 7: The identity of the streptokinase polynucleotide, from which the restriction map of Fig 7 is derived, should be stated.

Fig 18: The figure legend is objected to for having a single hard bracket –]– at the end.

Appropriate corrections are required.

Information Disclosure Statement

If Applicants wish for the 22 references cited in their response of November 23, 2005, pages 23-26, to be part of the file, they should check that said references have been submitted and cited in an Information Disclosure Statement.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 39, 40, 47-49, and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claims 37 and 49 are rendered indefinite by the phrase "the N-terminal region of SEQ ID NO: 2". Neither the claims nor the specification define the metes and bounds of

"the N-terminal region of SEQ ID NO: 2". Therefore, the skilled artisan would not be apprised of the recited invention.

Claims 39 and 51 are rendered indefinite by the phrase "said streptokinase component comprises amino acids 1-383 of SEQ ID NO: 2". It is unclear whether said phrase is meant to mean the streptokinase component consists of amino acids 1-383 of SEQ ID NO: 2, the streptokinase component comprises amino acids 1-383 but not 384-414 of SEQ ID NO: 2, or the streptokinase component consists of any polypeptide comprising amino acids 1-383 of SEQ ID NO: 2. The latter meaning would encompass residues 1-414 of SEQ ID NO: 2, the full-length protein. Claims 40 and 52, as dependent claims are rejected under 35 USC 112, second paragraph, for the same reasons. Clarification is required. For purposes of examination, it is assumed that said phrase is meant to mean "the streptokinase component comprises amino acids 1-383 but not 384-414 of SEQ ID NO: 2".

Claim 40 recites a polypeptide encoded by the polynucleotide of SEQ ID NO: 11, which comprises a coding region for residues 1-414 of SEQ ID NO: 2 (**see enclosed alignment**). However, Claim 40 is dependent from Claim 39, which recites the limitation of a polypeptide comprising residues 1-383 of SEQ ID NO: 2. Thus, it is unclear whether Claim 40 is meant to recite a polypeptide comprising residues 1-414 of SEQ ID NO: 2 or only residues 1-383 of SEQ ID NO: 2. Clarification is required.

For Claim 47 and 49, the phrase "a fibrin-binding component" renders the claims in definite. Claims 47 and 49 are dependent from Claim 34, which defines the fibrin-binding domains comprised by the polypeptide of Claim 34. It is unclear whether Claims 47 and 49

should read "the fibrin-binding component", referring to the fibrin-binding components defined in Claim 34 or whether Claims 47 and 49 are meant to mean "any fibrin-binding component". Claims 48 and 50-52, as dependent from Claims 47 and 49, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons. Clarification is required. For purposes of examination, it is assumed that Claims 47 and 49 are meant to refer to any fibrin-binding component.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The specification is enabling for the chimeric polypeptide encoded by the nucleic acid molecules set forth in Figs 17b, 19b, 21b, and 22b. However, the specification does not reasonably provide enablement for any chimeric polypeptide comprising any streptokinase component, wherein said chimeric polypeptide additionally comprises any linker region, wherein the linker region is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 34 is so broad as to encompass any chimeric polypeptide comprising any streptokinase component, wherein said chimeric polypeptide additionally comprises any linker region, wherein the linker region is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. Claims 35-54 provide addition limitations to the scope of chimeric polypeptides encompassed by Claim 34. However, all of said claims encompass chimeric polypeptides comprising a linker region is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of chimeric polypeptides, as broadly encompassed by the

claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired plasminogen activation and linker function requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the chimeric polypeptide as set forth in Figs 17b, 19b, 21b, and 22b.

While recombinant and mutagenesis techniques and plasminogen activation assays are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claim 34 which encompass any chimeric polypeptide comprising any streptokinase, or variant thereof, and any linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The specification does not support the broad scope of Claims 35-54 which encompass any chimeric polypeptide comprising a large number of streptokinase

polypeptides, or variants thereof, and any linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The specification does not support the broad scope of Claims 34-54 because the specification does not establish: (A) the structure of all streptokinase polypeptides that have the desired utility; (B) the structure of all linker polypeptides that have the desired utility; (C) regions of the streptokinase polypeptide's structure which may be modified without effecting the plasminogen activation; (D) regions of the linker polypeptide's structure which may be modified without effecting the ability to (i) prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component; (E) the general tolerance of the plasminogen activation to alterations in the structure of any streptokinase component and extent of such tolerance; (F) the general tolerance of the linker function to alterations in the structure of any linker peptide and extent of such tolerance; (G) a rational and predictable scheme for choosing any streptokinase or linker component, or modifying any residues thereof, of with an expectation of obtaining the desired biological function; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices of chimeric proteins is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of chimeric proteins comprising any streptokinase polypeptide and any linker region that is sufficiently flexible so as to (i)

prevent activation of plasminogen by said streptokinase component and (ii) so as to allow plasmin-dependent activation of the streptokinase component. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In anticipation of the instant rejection, Applicants provide the following arguments.

Applicants' initial remarks summarize the legal basis for rejection under 35 U.S.C. 112, first paragraph.

(A) Capon v Eshhar v Dudas, 418 F.3d 1349 (Fed. Cir. 2005) has clarified that 35 USC 112 does not require re-analysis in the specification of that which was already known. The Board's rule that the nucleotide sequences of chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, ***is an inappropriate generalization***. (Applicants' emphasis)

(B) ***It is not necessary that every permutation within a generally operable invention be effective*** in order for an inventor to obtain a generic claim. (Applicants' emphasis)

(C) The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. An extended period of experimentation may not be undue if the skilled artisan is given sufficient guidance. If the skilled artisan can readily anticipate the effect of a change within the subject matter, there is predictability in the art. (MPEP 2164)

(D) Flexibility of the adjoining region [linker] is a key factor for predicting the plasmin-dependent activation kinetics of the disclosed constructs. SK-FBD4,5 and SK-FBD1,2, comprising GGGQAQQIV and GGGQAQQMV linkers, respectively, had a 10 min and 10.5 min lag, respectively. Using the flexible region naturally existing at the N-terminus of streptokinase, IAGPQWLL, gave an 8 min lag. Use of the linkers IAGPQWLL and GGGQAQQIV within the construct FBD4,5-SK-FBD4,5, provided an 18 min lag. Thus, the flexible regions can be used to predictably control the kinetics of plasmin-dependent activation of streptokinase. The Examiner is reminded that the flexibility of a peptide can be predicted from amino acid composition and is not dependent on specific primary sequence.

(A) Reply: It is acknowledged that well known teachings in the art need not be re-analyzed in the specification. It is also acknowledged that the prior art enables the skilled artisan to make a chimeric fusion protein comprising human fibronectin-derived fibrin binding domains (FBD) 1 and 2 or 4 and 5 (Kornblihtt et al, 1984; pg 1755, parg 2). However, the genus of all streptokinase polypeptides capable of plasminogen activation is not well known in the art. Banerjee et al, 2004 clearly teach that, "Streptokinases produced by different groups of streptococci differ considerably in structure" (pg 291, parg 1). Moreover, the scope of the instant claims is not limited to polynucleotides encoding chimeric proteins comprising only naturally-occurring streptokinase polypeptides, but encompasses polynucleotides encoding any chimeric protein comprising any polypeptide having the function of streptokinase to activate plasminogen. Relevant thereto, Banerjee et al also teach that, "[R]esearch has focused on structurally modifying streptokinase" and

"Any structural change needs to be informed by a thorough structure-function analysis of streptokinase domains" (pg 292, parg 2). Thus, Banerjee et al teach that the structure of streptokinase polypeptides is highly variable and that the functional effects of altering the structure are unpredictable and must be tested experimentally.

The prior art fails to enable the skilled artisan to make and use any polynucleotide encoding a chimeric protein comprising a linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. Thus, the specification must enable the skilled artisan to make and use such polynucleotides. It is acknowledged that Example 3 teaches the making of a polynucleotide encoding a chimeric protein comprising the linker region, Gly-Gly-Gly, between an N-terminal streptokinase component and a C-terminal FBD4,5 component (SK-G_3-FBD4,5), while Example 4 teaches the making of a polynucleotide encoding a chimeric protein comprising the same linker region, Gly-Gly-Gly, between an N-terminal streptokinase component and a C-terminal FBD1,2 component (SK-G_3-FBD1,2). Examples 5 and 6 teaches the making of polynucleotides encoding chimeric proteins comprising an N-terminal FBD4,5 component and a C-terminal streptokinase component (FBD4,5- SK) and an N-terminal and C-terminal FBD4,5 component with a central streptokinase component (FBD4,5- SK-FBD4,5), respectively. It is noted that neither of Examples 5 and 6 teach that said chimeric proteins comprise a linker. It is also acknowledged that the specification teaches that activation of plasminogen by said constructs shows a lag of 10-12 mins for SK-G_3-FBD4,5 or SK-G_3-FBD1,2 a lag of 7-8 mins for FBD4,5-G_3- SK, and a lag of 20-25 mins for FBD4,5-

SK-FBD4,5, compared to no lag for native streptokinase (pg 55, parg 1). Based on said teachings a person of ordinary skill in the art would believe that, more likely than not, the lag time seen with the chimeric proteins vs the native streptokinase is not due to the presence or absence of a linker, but to the presence or absence of fibrin binding domains. Likewise, the skilled artisan would believe that the effect of plasmin on the lag period (pg 55, parg 2 – pg 56, parg 1) is, more likely than not, due to the presence or absence of fibrin binding domains, not the presence or absence of a linker. Thus, the specification has failed to enable the skilled artisan to make and use a polynucleotide encoding a chimeric protein comprising a linker region that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component because the linker appears to be irrelevant to said activation processes.

(B) Reply: The instant rejection is not based on the premise that every permutation within the recited invention be effective; but, is based on the fact that neither the specification nor the art enable the skilled artisan to make and use the full scope of the recited invention without undue experimentation. As explained in (A) above, (D) below, and the prior action, the specification fails to enable the skilled artisan to make and use any polynucleotide encoding any chimeric protein comprising any streptokinase polypeptide capable of plasminogen activation and any linker peptide that is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component.

(C) Reply: As explained in (A) and (B), above, undue experimentation would be necessary to practice the recited invention. Banerjee et al, 2004 teach that the structure of streptokinase polypeptides is highly variable and that the functional effects of altering the structure must be tested experimentally. Neither the art nor the specification provide guidance as to which polynucleotides, encoding which naturally-occurring streptokinase polypeptides, can be used for the desired function or the positions within said naturally-occurring streptokinase polypeptides where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility. Moreover, Banerjee et al, teach that the effects of changing any residues in any streptokinase polypeptide are unpredictable. As also explained in (A) and (B), above, neither the art nor the specification teach any linker having the required functional properties, or provide guidance on how to make and use such a linker. Undue experimentation would be required to make and test an essentially unlimited number of linkers for the properties of being sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. While recombinant and mutagenesis techniques and plasminogen activation assays are known, it is not routine in the art to screen an essentially unlimited number of chimeric proteins for the desired activity, as encompassed by the instant claims.

(D) Reply: The specification fails to distinctly assert that the specific peptides GGGQAQQIV, GGGQAQQMV, and IAGPQWLL function as flexible linkers in the recited chimeric proteins or to distinctly assert that said peptides (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation

of the streptokinase component. The specification also fails to provide evidence that (i) said linkers have differences in flexibility or (ii) that differences in flexibility is responsible for differences in the lag time for plasminogen activation. Hindsight reasoning cannot be used to provide evidence for enablement that is lacking in the specification as filed. Furthermore, as described above, the differences in lag times for plasminogen activation could be due to differences in the type, number, and/or position of the fibrin-binding domains. Moreover, Jackson et al, 1986 teach that a fragment of streptokinase consisting of residues 1-383 streptokinase exhibits a lag in activation of plasminogen (Fig 4), suggesting that a "flexible linker" is not necessary for regulating the initial rate of plasminogen activation.

For these reasons, Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Written Description

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claims 34 and 47 introduce the limitation of "a region that is sufficiently flexible so as to prevent activation of plasminogen by said streptokinase component". The specification fails to describe said limitation and, thus, Claims 34 and 47, as well as dependent Claims 35-46 and 48-54, are rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Claims 34-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of chimeric proteins comprising any streptokinase polypeptide capable of plasminogen activation and a linker peptide, wherein the linker peptide is sufficiently flexible so as to (i) prevent activation of plasminogen by the streptokinase component and (ii) allow plasmin-dependent activation of the streptokinase component. The specification teaches the structure of no representative species of such chimeric proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality being a chimeric protein that can, due to the flexibility of the linker, activate plasminogen only after a lag. Given this lack of description of the structure of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicants' arguments that are relevant to the instant rejection, and the Examiner's responses, are presented above under the enablement rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Prior rejection of Claims 3, 32, and 33 under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996 is rendered moot, as said claims have been cancelled.

Claims 34-37, 41, and 42 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Dawson et a, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996. Malke et al teach a fusion protein comprising streptokinase and the fibrin binding domains from plasminogen, while Dawson et al teach a fusion protein comprising a streptokinase component and an intergenic linker that promotes thrombus-specific activation of streptokinase (col 2, parg 1). Neither Malke et al nor Dawson et al teach a fusion protein comprising streptokinase and either or both of the fibronectin-derived 1/2 or 4/5 fibrin binding domain pairs. Matsuka et al teach the structure of fibrin binding domains 1-5 of fibronectin and that domains 4 and 5 form the critical fibrin-binding site of fibronectin (pg 9544, parg 2; Fig 9). It would have been obvious to a person of ordinary skill in the art to use the method of Malke et al or Dawson et al to prepare a fusion protein comprising streptokinase linked to the fibrin binding domains 4/5. Motivation to do so is provided by Dawson et al wherein they teach the following. Fibrinolytic therapy using streptokinase and other plasminogen activators has become widespread (col 1, lines 39-42). A major problem with these agents is that they are not thrombus specific, as they activate plasminogen in the general circulation (col 1, lines 49-52). An approach to enhancing fibrinolysis and inhibition of blood clotting is based on the use of fusion proteins that are activated specifically at the site of blood clotting (col 2,

lines 1-5). Goldstein et al teach that one method of targeting streptokinase activity to the site of blood clotting is to use a fusion protein comprising streptokinase and an anti-fibrin antibody (Fig 6). A person of ordinary skill in the art would know that the fibrin binding domains of fibronectin would serve the same targeting function as the anti-fibrin antibody of Goldstein et al. Furthermore, the skilled artisan would be motivated to construct a chimeric protein comprising streptokinase and the fibrin-binding domains 4/5 at both the N- and C-terminal end in order to increase the affinity of the chimeric protein for fibrin. Therefore, based on the problem to be solved, the state of the art, and knowledge of the skilled artisan, Claims 34-37, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996, while Claim 39 is rejected over said combination and further in view of Jackson et al, 1986. Chimeric proteins rendered obvious by the combination of Malke et al, Dawson et al, Matsuka et al, and Goldstein et al are described above. Matsuka et al further teach that fibronectin is covalently linked to fibrin via Factor XIII transglutaminase activity (pg 9439, parg 1), while Dawson et al further teach a streptokinase chimeric protein comprising a linker that is a target for cleavage by Factor XIII transglutaminase (col 2, parg 1). It would be obvious to a person of ordinary skill in the art to include, within the chimeric proteins described above, a linker that is a target for Factor XIII transglutaminase. Motivation to do so derives from the desire to covalently

attach the streptokinase component to the fibrin clot in order to stably target the clot for activation of plasminogen. The combination of Malke et al, Dawson et al, Matsuka et al, and Goldstein et al fails to teach a streptokinase component comprising residues 1-383 of streptokinase. Jackson et al teach that a polypeptide consisting of residues 1-383 of streptokinase activates plasminogen after a lag (Fig 2). It would be obvious to a person of ordinary skill in the art to modify the polypeptides above to comprise residues 1-383 but not residues 384-414 of streptokinase. Motivation to do so derives from the desire to limit activation of circulating plasminogen and promote the activation of clot-associated plasminogen upon binding of the chimeric protein to fibrin. The expectation of success is high, as methods for making recombinant proteins are well known in the art. Therefore, Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994 and further in view of Goldstein et al, 1996, while Claim 39 is rejected over said combination and further in view of Jackson et al, 1986.

Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein et al, 1996. As described above, Goldstein et al teach a chimeric protein comprising streptokinase and an N-terminal fibrin-binding domain that is an anti-fibrin antibody (Fig 6). The chimeric protein of Goldstein et al exhibits a lag in the activation of plasminogen (Fig 4). Goldstein et al do not teach a chimeric protein comprising streptokinase and a fibrin-binding domain at both the N- and C-terminal. As explained in the prior action and above, the use of fusion proteins that are active specifically at the site of blood clotting would be advantageous for fibrinolytic therapy using streptokinase.

Based on the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art, it would have been obvious to a person of ordinary skill in the art to use the methods of Goldstein et al to modify their chimeric protein such that the fibrin binding domain is at both the N- and C-terminal. Motivation to do so is based on the desire to optimize the binding of the chimeric protein to fibrin. The expectation of success is high, as methods for making chimeric proteins are well known in the art. Therefore, Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein et al, 1996.

Claims 43-45 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994, Goldstein et al, 1996, and Jackson et al, 1986 and further in view of Johnson et al, 1996. Chimeric proteins rendered obvious by the combination of Malke et al, Dawson et al, Matsuka et al, Goldstein et al, and Jackson et al are described above. Said combination does not teach chimeric proteins comprising a -Gly-Gly-Gly- linker. However, the use of the peptide -Gly-Gly-Gly- as a linker is well known in the art. For example, Johnson et al, 1996 teach using said peptide as a linker for proteins designed to study ribonuclease T1 (pg 10223, parg 3). It would be obvious to a person of ordinary skill in the art to include, within the chimeric proteins described above, a -Gly-Gly-Gly- linker. Motivation to do so derives from the fact that said peptide is very flexible (Johnson et al; pg 10223, parg 3) and the desire to provide a flexible linker between the streptokinase component and the fibrin-binding domain component in order to avoid functional interference between the two components. The expectation of success is high, as methods for making recombinant

proteins comprising linkers are well known in the art. Therefore, Claims 43-45 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994, Goldstein et al, 1996, and Jackson et al, 1986 and further in view of Johnson et al, 1996.

Claim 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994, and Goldstein et al, 1996 and further in view of Kobayashi et al, 1991. Chimeric proteins rendered obvious by the combination of Malke et al, Dawson et al, Matsuka et al, and Goldstein et al are described above. Said combination does not teach pharmaceutical compositions comprising the chimeric proteins and either human serum albumin or mannitol. However, it is known in the art that human serum albumin or mannitol can be added to pharmaceutical compositions to stabilize enzymes (Kobayashi et al; col 1, parg 5-6). It would be obvious to a person of ordinary skill in the art to include human serum albumin or mannitol in pharmaceutical compositions comprising the chimeric proteins rendered obvious to a person of ordinary skill in the art by the combination of Malke et al, Dawson et al, Matsuka et al, and Goldstein et al. As stated above, motivation to do so is provided by the desire to stabilize the enzymatic activity. The expectation of success is high, as pharmaceutical compositions comprising enzymes and human serum albumin or mannitol are well known in the art. Therefore, Claim 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malke et al, 1993 or Dawson et al, 1995 in view of Matsuka et al, 1994, and Goldstein et al, 1996 and further in view of Kobayashi et al, 1991.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants identify support, within the original application, for any amendments to the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1656